EXHIBIT 3

EXPERT REPORT, ANNA LEMBKE, M.D.

March 25, 2019

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry's hidden role.[57]

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the 'undertreatment of pain.' Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk. Further, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

a. Scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."[58] Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:

i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.[36] (p. 8) Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks or months to manifest, and duration of exposure is the most significant risk factor for addiction (see discussion of Edlund study,[20] above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers, (the

[57] PDD8801183361- PDD8801183364 at 3363

[58] Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Pain*. 2009;10(2):113-130 at p. 130.e5.

molecular equivalent of heroin), requires a longer period of study than 12 weeks.

ii. There are serious and certain risks associated with long term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, depression, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long term opioid therapy.[59] These risks increase with increasing dose and duration of the drug.[60] Hence, the high risks associated with opioids, necessitate a longer study period to assess the true benefit-risk ratio for all patients.

b. A series of reviews, including several in the Cochrane Database, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.

i. The 2010 Cochrane (Noble 2010) review found that there was only "weak" evidence to support the use of opioids for chronic non-cancer pain.[61]

A. "All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias." Reasons for this assessment included the funding source ("Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (e.g., drug company) [p. 9]," failure to compare characteristics of dropouts to those of patients who completed the studies; and failure to describe recruitment methods. The highest risk of bias existed for the "continuous outcomes" of pain relief and quality of life, because "high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes."[62]

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[59] Lembke *et al.*, "Weighing The Risks," fn. 3, above, at p. 985; *see also* Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evid Rep Technol Assess (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPCERTA218 at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. JAMA Internal Medicine. 2018, at p. 298.

[60] Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4). doi:10.7326/M14-2559, p. 283

[61] Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.

[62] *Id.* at pp. 7-8.

B. At pp. 9-14, specific data on attrition were provided: For the "strong opioid" category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects and 10.3% discontinued due to insufficient pain relief, for a total of 44.4% who discontinued strong oral opioids.[63]

C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all 3 oral opioid studies. "Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased."[64]

D. The authors report pain relief for those able to remain on oral opioids for 6 months; however: "The strength of the evidence supporting this conclusion is weak."[65]

E. Quality of Life (QoL):

I. For oral morphine: A single study (Allan, 2005), reporting a "small improvement on the mental subscale and a larger improvement of the physical subscale" provided an "insufficient quantity of data from which to draw conclusions."[66]

II. QoL improvement was "weakly supported" with transdermal fentanyl (TDF).[67]

III. For QoL with intrathecal opioids, there were inconsistent findings "No conclusions can be drawn."[68]

F. "Data describing long-term safety and efficacy of opioids for CNCP are limited in terms of quantity and quality. An evidence base consisting of low-quality studies provides only *weak evidence* from which to draw qualitative

[63] *Id.* at pp. 9-14.
[64] *Id.* at p. 15.
[65] *Id.* at p. 16.
[66] *Id.* at p. 20.
[67] *Id.* at p. 21
[68] *Id.* at p. 22

conclusions and only low-stability evidence from which to draw quantitative conclusions." (Emphasis added.)[69]

G. "Despite the identification of 26 treatment groups with 4768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions."[70]

ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, "There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo."[71] (Emphasis in original.)

A. "The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks."[72]

B. "There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP…. We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants."[73]

iii. Another Cochrane review (McNicol 2013) found: "While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice."[74] Note that the McNicols review defined "intermediate" term studies as 35-84 days (ie, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12

[69] *Id.* at p. 23.
[70] *Id.* at p. 25.
[71] Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013. doi:10.1002/14651858.CD004959.pub4, at p. 2
[72] *Id.*
[73] *Id.*
[74] McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev*. 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain.[75]

iv. Another 2014 Cochrane review reached similar conclusions: "Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that most of the trials included in our review had a treatment duration of several days or a few weeks only."[76]

A. "Although some of the newer trials in the update had slightly longer treatment durations [cites omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted]"[77](emphasis added).

B. Reviewers found that the "small mean benefit" was "contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence interval] did not include the minimally clinically important difference" on a visual analog scale.[78]

v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: "Evidence is *insufficient* to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms." [79] (Emphasis added.) The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. "We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack

[75] *Id.* at p. 13.
[76] da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip (Cochrane Review). 2014, at p. 28.
[77] *Id.*
[78] *Id.* at p. 2.
[79] Chou *et al.*, "Effectiveness and Risks – Systemic Review," fn. 60, above, at p. 276.

of non-opioid comparison group and heterogeneity of the results."[80]

vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."[81]

vii. In another systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids "remains limited to short term trials showing modest effects versus placebo for chronic low back pain." Shortcomings of the studies included high attrition (30-60% in most trials) and "short follow-up" (one at 16 weeks, all others shorter).[82] Authors also noted: "Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate harms." [83] (See paragraphs 9a-d, below, for discussion of enriched enrollment study design).

viii. In a systematic review and meta-analysis (Häuser, Schmerz, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state "… the risk of bias [for these studies] was high …. all studies were funded by the manufacturers of the drugs[84]…. average pain scores are unrepresentative of patient experience and of very limited utility[85]…. The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or

[80] *Id.* at p. 280
[81] Chou, *et al.*, "Clinical Guidelines," fn. 58, above, at p. 130.e5.
[82] Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. Ann Intern Med. 2017. doi:10.7326/M16-2458, at p. 483.
[83] *Id.* at p. 486.
[84] Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. Schmerz. 2015. doi:10.1007/s00482-014-1452-0, at p. 4.
[85] *Id.* at p. 7

mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care."[86]

ix. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate and prefer opioids, and hence are not reflective of the general clinical population.

A. Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),[87] and hence were biased toward favoring opioids. Open-label continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.

B. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002), 222 subjects were assigned to opioid groups and 73 were assigned to placebo.[88] A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,[89] and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of subjects who had demonstrated the capability to tolerate opioids, and the study's claims of

[86] *Id.* at p. 8.
[87] Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. J Pain Res. 2018. doi:10.2147/JPR.S160255, at pp. 923-934
[88] Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage. 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283
[89] *Id.* at p. 283.

efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.[90]

C. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: "The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported."[91]

c. A recent (Busse 2018) metaanalysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.[92]

i. The primary study outcomes were "pain relief, physical functioning, and vomiting".[93] The study defined the term Minimally Important Difference (MID) as "the smallest amount of improvement in a treatment outcome that patients would recognize as important."[94] The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.[95]

ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.[96] Despite not meeting the standard, the authors state, "Although the difference did not meet the minimally important difference of 1 cm, opioids were

[90] *Id.* at p .286.
[91] Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.
[92] Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472.
[93] *Id.* at p. 2449.
[94] *Id.* at p. 2450.
[95] *Id.* at pp. 2451, 2455.
[96] *Id.* at p. 2451.

associated with pain relief compared to placebo…."[97] A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study's own definition of a clinically significant difference.. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for "role functioning;" however, "[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo."[98]

iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.[99]

iv. As for "Active Comparator" studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed "no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief," (emphasis added), and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74, $p \leq 0.001$).[100]

v. Although the goal was to assess "chronic" non-cancer pain, the authors acknowledge that "it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months."[101] (Emphasis added). There is some inconsistency in the literature about the definition of "chronic." For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of "pain which persists past the normal point of healing," considered to be 3 months[102]; however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed "Chronic opioid use…".[103] In any case, the Busse authors' statement that it could not be applied to "long-term" use is an important limitation.

vi. The Busse study states, "Studies with longer follow-up reported less relief," which provides significant support for the reduced pain

[97] *Id.* at pp. 2451-2452.
[98] *Id.* at pp. 2451, 2455.
[99] *Id.* at p. 2455.
[100] *Id.*
[101] *Id.* at p. 2457.
[102] Noble, *et al.*, "Long Term Opioid Management," fn 61, above, at p. 2.
[103] *Id.* at pp. 3, 6.

relief of opioids over time, and which buttresses the conclusion that even the minor "improvements" in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days' follow-up,[104] cannot be extrapolated to longer term opioid use.

vii. Three quarters of the studies 76 (79%) reported receiving industry funding.[105]

viii. Despite these limitations, the authors concluded: "… some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids." The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.[106]

ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for "benefits" that are found to be comparable to placebo for the large majority of subjects studied.

x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.[107] Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.

d. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.[108]

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[104] Busse, *et al.*, "Opioids for Chronic Noncancer Pain," fn 92, above, at p. 2451.
[105] *Id.* at p. 2451.
[106] *Id.* at p. 2456.
[107] Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. 2017. doi:10.1186/s12916-016-0775-3, at p. 10.
[108] Krebs EE, Gravely A, Nugent S, *et al.* Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. JAMA - J Am Med Assoc. 2018. doi:10.1001/jama.2018.0899

i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.[109]

ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long term opioid therapy in real-life.[110] Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.[111] It was not sponsored by an opioid manufacturer.[112]

iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable. Further, other studies have shown that opioids are no better than non-opioids for pain treatment.

A. In the Cochrane Review by Chaparro, *et al.* , discussed above, opioids were not superior to non-opioids for chronic low back pain.[113]

B. In a review of randomized head to head comparisons of opioids vs non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12

[109] *Id.* at p. 872.
[110] *Id.* at p. 873
[111] *Id.* at p. 875.
[112] *Id.* at p. 881.
[113] Chaparro, *et al.*, "Opioids Compared to Placebo," fn 71, above, at p. 2.

weeks) therapy of neuropathic, low back, and osteoarthritic pain.[114]

C. A systematic review comparing oral NSAIDS with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.[115]

e. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing, by claiming that the 'failure' to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like The Joint Commission. In their promotional material and "Train the Trainer" course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to Joint Commission and legal sanctions. Below are just a few examples. (See Appendix I for more detail.)

i. I remember that fear of 'undertreating pain' permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board, and lawsuits that could follow, if they denied a patient's request for opioids.

ii. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Opioid Industry, which he referred to as "narcopharma. The American Pain Society, in turn, supported University of Wisconsin Pain and Policy Study Group (PPSG) professors David Joranson and June Dahl to "visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain."[116]

iii. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report.

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[114] Welsch P, Sommer C, Schiltenwolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. Schmerz. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

[115] Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. Osteoarthr Cartil. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

[116] Saper, "The Influence of Pharma," fn 38, above, at p. 9.

Those documents show substantial contributions by Purdue Pharma, Janssen, Endo, Ortho-McNeil, Alpharma, and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).

iv. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt intractable pain laws that encouraged opioid prescribing by shielding physicians from liability. Although the statutes may have initially been intended for cancer, acute, and end-of-life pain, the statutes do not necessarily include any such limitations, and the Ohio statute did not restrict its protective shield to those circumstances. Intractable Pain Laws in various states, including Ohio,[117] strengthened physicians' ability to prescribe opioids and also protected physicians from disciplinary action if the drugs were prescribed in compliance with the terms of the law.

v. Ohio's Intractable Pain Law has since been revised to include a more involved series of steps that a prescribing doctor should take regarding discussion of the risks, monitoring the results, etc. Such belated restrictions were, however, insufficient to unwind the damage done by prior enactment of legislation that encouraged the increased prescribing of opioids. Notably, the PPSG documents include Ohio among the states whose pain laws were "improved" between 2000-2003, where "improvement" included loosening restrictions on opioid prescribing. (See Appendix II).

f. Pain *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.

i. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores. The authors concluded, "this systemic review suggests that pain, function and quality of life may improve during and after opioid dose reduction."[118]

[117] Ohio Admin. Code §4731-21

[118] Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. Pain Med (United States). 2016. doi:10.1093/pm/pnv079, at p. 14.

ii. A meta-analysis of opioid legacy patients (patients on long term opioid therapy as a 'legacy' of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).[119] The authors repeatedly note the need for more research and better quality evidence. Nonetheless, they conclude "several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction."[120]

iii. In a study by Sullivan et al, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).[121] The authors write, "It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0–10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction ."[57122]

iv. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg

[119] Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. Ann Intern Med. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.
[120] *Id.* at p. 181.
[121] Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. J Pain. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.
[122] *Id.* at p. 318.

(P = .002). Of note, neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction.[123]

v. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death. [124] Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.

g. Just as increased prescribing has been the cause of increased consumption and risk,[125] decreasing opioid prescribing decreases opioid consumption and risk. When doctors prescribe fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users.

i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids.… Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."[126]

ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an "ultrarestrictive opioid prescription protocol" (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire

[123] Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. JAMA Intern Med. 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

[124] Gomes T, Mamdani MM, Dhalla I a, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686. See also Lembke *et al.*, Weighing The Risks," fn 3, above, at p. 982; Edlund *et al.*, Role of Opioid Prescription," fn 25, above, at p. 7; Chou *et al.*, "Effectiveness and Risks," fn 60, above, at p. ES-1.

[125] Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. JAMA Surgery. 2018, at p. E6.

[126] Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. JAMA Otolaryngology - Head and Neck Surgery. 2018, at p. 1102.

perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.[127]

A. The authors write, "For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation (P < .001). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation (P < .001). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naive patients (P < .001)."[128]

B. "The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; P = .99), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; P = .06), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; P = .15)."[129]

h. In sum, the evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,[130] was never more than "weak." Such "weak evidence" was never sufficient to justify the aggressive promotion and resulting exponential increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence[131] that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.[132] "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. Finally, and confirming the consensus of independent scientists, according to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management

[127] Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. JAMA Netw Open. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.
[128] *Id.* at p. 1.
[129] *Id.* at pp. 1-2.
[130] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 Cases. Pain. 1986;25(2):171-186.
[131] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn 114, above, at p. 3.
[132] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 880.

and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management* (VonKorff *et al.* , 2011)."[133] (Emphasis added).

5. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 40%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed.

a. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance. The current opioid epidemic is the most tragic and compelling example of that fact in modern history. As opioid prescribing has increased, and opioids have become more accessible to all Americans, opioid use has increased, and with it the rates of opioid addiction. The nearly quadrupling of opioid prescribing between 1999 and 2012 does not merely correlate with rising rates of opioid addiction and related deaths. It is causative. In their 2017 report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use," The National Academies of Science, Engineering and Medicine stated, that despite FDA's instruction to the panel that its task was not to assign blame for the current situation, "*certain hypotheses about causes of the epidemic are inescapable.* For example, the data presented earlier in this chapter make a prima facie case that *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms."[134] (emphasis added)

b. Likewise, decreased exposure to addictive substances decreases risk of addiction. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number

[133] National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.*; 2017. doi:10.17226/24781, at p. 29.
[134] *Id.* at pp. 40-41.

of Americans consuming and becoming addicted to alcohol.[135] (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.[136]

c. There is a clear link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (NMUPO), is defined as taking an opioid medication other than prescribed. With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer duration (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, and addiction.

i. In 2016, according to the National Survey on Drug Use and Health (NSDUH), more than 11 million Americans misused prescription opioids.[137] More than half obtained the misused prescription opioids from a friend or family member, who in most cases obtained them from a doctor. Thirty-five percent obtained misused prescription opioids directly from a single prescriber. Less than 10% of Americans misusing prescription opioids got them from a 'street dealer.'[138] In other words, a medical prescription is the primary conduit for prescription opioid misuse. It should be noted that NSDUH data, by definition, are based on "households" and, as such, the data do not take into account misuse among homeless or incarcerated populations.

ii. The scientific literature shows that most lifetime nonmedical users of prescription opioids reported a lifetime history of medical use of prescription opioids, that is, most nonmedical users had current or previous legitimate prescriptions. "After controlling for other factors (e.g., gender, race, etc.) we observed an eight-fold increase (OR = 8.1, $p < 0.001$) in lifetime nonmedical use and a 10-fold increase (OR = 9.8, $p < 0.001$) in past year nonmedical use among

[135] Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.
[136] Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.
[137] Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD, at Table 1.97A.
[138] *Id.* at Table 6.53B.

students who had either current or previous prescriptions for pain medication."[139]

iii. Teens are especially vulnerable to opioid misuse. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months,[140] an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and marijuana. They rank second among teens. Among teens who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.

iv. McCabe *et al.* conducted a prospective national study of high school seniors in the U.S. to identify the sequence of medical versus non-medical use of prescription opioids, and the later development of a substance use disorder (addiction). They found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.[141]

A. These data show that teens who are exposed to prescription opioids without a prescription, will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life. The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.[142]

B. The authors write, "These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents."[143] While the authors suggest that screening can play a role in mitigating future opioid addiction,

[139] Boyd CJ, Esteban McCabe S, Teter CJ. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. Drug Alcohol Depend. 2006. doi:10.1016/j.drugalcdep.2005.05.017, at p. 7.
[140] Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD; 2013., at p. 53.
[141] McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend*. 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.
[142] *Id.* at p. 381.
[143] *Id.* at p. 383.

screening tools have been shown to have limited efficacy in identifying at risk patients.[144] The more significant goal is to reduce unnecessary and excessive opioid prescribing, which increases risk by increasing exposure to both medical and subsequent non-medical use.

d. Even very limited exposure can result in addiction. A recent study of 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%.[145] This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.

e. There are dozens of articles in the scientific literature that provide data on the risk of addiction, dependence, and/or misuse of prescription opioids in the course of medical treatment. In my opinion, these sources, individually and collectively, likely provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:

i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.

ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.

iii. Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.

iv. Many studies are too short to assess addiction risk.

A. The natural history of addiction is that it takes some time to develop. Many people who become addicted start out using that substance to solve a problem, from anxiety to insomnia to physical pain. Over time, they become addicted to that substance. Although some become addicted very quickly, most become addicted over months to years, rather than days to weeks.

[144] Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. Pain Med. 2018;19(7):1382-1395. http://dx.doi.org/10.1093/pm/pnx332, at p. 1382.

[145] Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. JAMA Intern Med. 2018, at p. E6.

B. Risk of addiction to opioids increases with dose and duration of an opioid prescription. The higher the dose, and the longer patients are on them, the more likely they are to misuse opioids and become addicted. As previously stated, for low dose (1-36 MMEs per day) chronic exposure to prescribed opioids (*i.e.,* longer than 90 days), the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[146] Because of the extraordinary increased risk of OUD with longer exposure, short-term studies are particularly ill-suited to assess that risk accurately.

C. Naliboff et al, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, "carefully selected" as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.[147] Urine toxicology screens were included in the protocol.[148] The authors concluded, "Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration*."[149] (emphasis added)

v. Many studies do not use rigorous detection methods

A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (below).

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[146] Edlund *et al.*, "Role of Opioid Prescription," n 25, above, at pp. 559-560.
[147] Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain. 2011;12(2):288-296. doi:10.1016/j.jpain.2010.09.003, at p. 288.
[148] *Id.* at p. 291.
[149] *Id.* at p. 295.

B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found that 43% of patients had a "problem" with opioids: positive urine toxicology or one or more aberrant drug taking behaviors. The authors concluded "Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone."[150]

C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. "Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use….Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs."[151] In other words, rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.

D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, 'doctor shopping,' and other indicators of misuse and addiction.[152]

vi. Taking into account these limitations, it is my opinion that a 2015 article by Vowles, *et al.* , nevertheless provides the most reliable pooled estimate of the risk of addiction with chronic opioid

[150] Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg. 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.
[151] Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. J Pain. 2007. doi:10.1016/j.jpaa.2012.02.008, at pp. 580-581.
[152] https://www.cdc.gov/drugoverdose/pdmp/states.html

therapy.[153] In particular, the Vowles data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to asses misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies. (By contrast, Fishbain et al, described below, completely excluded studies that did not meet their quality standards, which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest. (By contrast, Fishbain was an expert witness for Purdue in at least 3 cases between 2005-2008.[154]) Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles' analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.

vii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies.(p. 572) Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).[155]

viii. Even the lower risk classification of 8-12% would be considered a "very common" risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:[156]

A. Very common >= 1/10

B. Common >= 1/100> and < 1/10

C. Uncommon >= 1/1000 and < 1/100

D. Rare >= 1/10,000 and < 1/1,000

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[153] Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. Pain. 2015. doi:10.1097/01.j.pain.0000460357.01998.f1.

[154] Graves v. Purdue Pharma (N.D. Miss. 2008), Rule 26(a)(2) Disclosure of David A. Fishbain, M.D., 8/21/08, at pp. 1-8.

[155] Vowles *et al.*, "Rates of Opioid Misuse," fn 153, above, p. 573.

[156] World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.

E. Very rare < 1/10,000

F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: "rare" in US labels is commonly < 1/1000; "Infrequent" is >1/1,000 to < 1/100; and anything over 1/100 is "frequent."[157]

ix. Vowles' definition of "misuse" as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder. As such, the prevalence of opioid use disorder in Vowles' review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD. (This is reasonably consistent with the Boscarino, *et al.* study[158] described below.)

x. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.[159]

A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).[160]

B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of 12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were asked to withdraw due to investigator assessment of "high risk level for drug

[157] Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. Pharmacol Res Perspect. 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.
[158] Boscarino J a, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.
[159] Brown J, Setnik B, Lee K, *et al.* Assessment , stratification , and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. 2011;(December). doi:10.5055/jom.2011.0088.
[160] *Id.* at p. 468.

abuse/misuse" after enrollment, and another 5% for "noncompliance."[161]

C. The Vowles analysis incorporates the Brown study's assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the "misuse" column.[162]

D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in his analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.[163] By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the "2-6%"rate of aberrant drug related behaviors reported by the investigators[164] and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.[165]

E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.

F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.[166]

xi. Also included in the Vowles analysis was a study by Fleming, *et al.* , again highlighting the discrepancy between self-report and urine toxicology.[167]

A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the population analyzed in the Fleming article

[161] *Id.* at p. 473.
[162] *Id.* at p. 572.
[163] *Id.* at p. 475, figure 2.
[164] *Id.* at p. 476.
[165] *Id.* at pp. 478-479.
[166] *Id.* at p. 481.
[167] Fleming, *et al.*, "Substance Use Disorders," fn 151, above, at p. 579.

discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence, using DSM-4 criteria[168] and Vowles incorporated these percentages into the data synthesis.

B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.[169] As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.[170]

C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients had more than expected (evidence of overuse), or opioids that were not prescribed (evidence of overuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).

D. Fleming also reported that "the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%)."[171]

E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the "3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians."[172] I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would

[168] *Id.* at p. 573.
[169] *Id.* at p. 574.
[170] *Id.* at p. 579.
[171] Fleming, *et al.*, "Substance Use Disorders," fn 151, above, at p. 573.
[172] *Id.* at p. 581.

alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.

f. Boscarino, *et al.* published a study of addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).[173] The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice; that drug-use disorder was assessed based on the final DSM-5 criteria; and that subjects were identified through drug orders in the electronic health records, not based on patient self-report or treatment record. Weaknesses include the low survey response rate (33%).[174]

i. "Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of "any" prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0)."[175]

ii. "A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment."[176]

iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles' definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles' definition of

[173] Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. Subst Abuse Rehabil. 2015:83. doi:10.2147/SAR.S85667, at p. 83.
[174] *Id.* at p. 86.
[175] *Id.* at p. 83.
[176] *Id.* at p. 83.

misuse. Accordingly, the totals of 13% "moderate to severe opioid use disorder" in Boscarino are consistent with Vowles' findings of 8-12% "addicted"; further, Vowles' finding of 21-29% "misuse" is reasonably consistent with Boscarino's report of 28% with "mild opioid use disorder." In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

g. The 2008 review by Fishbain claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.[177] Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%, rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.

i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.

ii. Fishbain's pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.[178]

iii. Fishbain's 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, Anesthesia 1981; 36:597-602,[179] (reported 16% addiction in Fishbain's 1992 article[180]), and Katon, Am J Psychiatry 1985;

[177] Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. Pain Med. 2008;9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

[178] *Id.* at p. 450.

[179] Evans PJD. Narcotic addiction in patients with chronic pain. Anaesthesia. 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

[180] The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain's 1992 article states, "Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction." (Fishbain 1992, Table 4, at 83; emphasis

142:1156-60, (reporting 18.9% addiction)[181], both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, Mayo Clinic Proceedings 1976; 54:241-4, [182] which reported an incidence of 24% addiction among a chronic pain population.[183] Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.

iv. Fishbain made an admittedly "arbitrary" decision to apply a 65% "quality score" requirement, despite his own reference to a source stating that studies with scores below 50% are generally not used.[184] The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.

v. A study reviewed by Fishbain (Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the pain assessment and documentation tool. J Opioid Manage 2005; 1:5.), was co-authored by Portenoy.[185] In this study, 27 physicians who attended training sessions to serve on "a pain-oriented speakers' bureau" applied a "Pain Assessment and Documentation Tool" (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.[186] The physicians reported their assessment that 5.93% (23/388) of

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added). Thus, comparing the two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain's 1992 study explicitly studied "Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*," (emphasis added); thus the figure of 16% (9/56) appears accurate.

[181] Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. Am J Psychiatry. 1985;(October):1156-1160, at p. 1157.

[182] Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

[183] Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. Mayo Clin. Proc. 1979 (April):241-244, at p. 242.

[184] Fishbain, *et al.*, "What Percentage," fn. 177, above, at p. 448.

[185] Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. J Opioid Manag. 2005.

[186] *Id.* at p. 258.

their patients were addicted.[187] However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more "aberrant drug-taking behaviors," such as requests for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.[188] Their conclusion of 5.93% addicted lacks validity for several reasons.

A. Appendix 1 states: "Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/ addition [sic]."[189] This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.

B. Other studies on Fishbain's reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors' reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study's summative results (5.93% + 19.3% +10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study[190] described above.)

C. The possibility of underestimating addiction rate is of particular concern in light of the participating physicians' roles as Speakers' Bureau trainees.

vi. In another study reviewed by Fishbain et al, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (Two and a half days each).[191] "When asked 'Do you have any drug craving?' (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any," during

[187] *Id.* at p. 263.
[188] *Id.* at pp. 260-261.
[189] *Id.* at Appendix I, p. 47.
[190] Boscarino, *et al.*, "Opioid-use disorder," fn 173, above, at p. 83.
[191] Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med. 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

the period of cessation of opioids.[192] Authors concluded from these data "that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use."[193] Appendix 1 states: "0% demonstrated psychological dependence."[194] This conclusion lacks validity for several reasons.

A. The short duration without opioids is insufficient to assess the presence of addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.

B. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about "craving" is likely to bias their response: 'craving' is a loaded term associated with addiction. Patients would be savvy enough to want to avoid this pejorative label.

C. This British study was funded by Janssen-Cilag, introducing inherent bias.[195]

D. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain's inclusion of an almost absurdly brief study of 60 hours of exposure – not even enough time to develop dependence, let alone addiction—while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.

h. Higgins, *et al.* performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,[196] but their findings need to be considered in light of a number of limitations.

i. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of

[192] *Id.* at p. 116.
[193] *Id.* at p. 119.
[194] *Id.* at Appendix 1.
[195] *Id.* at p. 113.
[196] Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth. 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids.

ii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.

iii. The authors claimed that the pooled rate was higher for the studies of "weak" opioids than for "strong" opioids because the subjects might have displayed "pseudoaddiction,"[197] i.e., because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and more bad outcomes.

iv. The authors' restrictive criteria resulted in only 12 studies having been included[198] compared to others (e.g., Vowles), who included 38 studies.

v. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%),(p. 1342) when in fact Vowles reported rates of addiction as 8-12%,[199] or approximately 21-29% when the spectrum of mild through severe OUD is included.

vi. Two of three authors report pharma consulting, including Pfizer.[200]

i. The 2010 Cochrane Review by Noble *et al.* (2010) claimed that opioid addiction occurred in "0.27% of participants in the studies that reported that outcome,"[201] and "… serious adverse events, including iatrogenic opioid addiction, were rare."[202] These findings are specious for the following reasons:

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[197] *Id.* at p. 1343.
[198] *Id.* at p. 1335.
[199] Vowles, *et al.*, "Rates of Opioid Misuse," fn 153, above, at p. 569; McNicol, *et al.,* Cochrane Review 2013, fn 74 at p. 28.
[200] Higgins, *et al.*, "Incidence of Iatrogenic," fn 196, above at p. 1343.
[201] Noble, *et al.*, "Long Term Opioid Management," fn. 61, above, at p. 9.
[202] *Id.* at p. 2.

i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.[203] Only 8 of the 26 included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.

ii. Only one of these studies (Portenoy, 2007)[204] was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were sponsored and/or written by industry authors, raising conflict of interest and bias issues.

A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.[205] Classification as 'opioid naïve' was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.[206] Opioid misuse and addiction did not warrant listing in the Adverse Event "Table 8."[207] In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events. Yet the authors claimed "Addiction was not reported as an adverse event for any participant."[208] The authors further stated "No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison et al, Spine 1998]."[209] The authors' conclusions are not reliable based on methodology inadequacies to assess for addiction risk.

[203] *Id.* at p. 1.
[204] Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. Clin. J. Pain 2007; 23: 287-299.
[205] Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naıve Patients With Chronic Low Back Pain. 2005;30(22):2484-2490, at p. 2484.
[206] *Id.* at p. 2485.
[207] *Id.* at p. 2488.
[208] *Id.*
[209] *Id.* at p 2489.

Even when investigators are attempting to detect addiction and abuse, as in the studies described above, the difficulties are daunting, as indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.[210]

B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.[211] Patients with "psychopathological or substance abuse problems" were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder. The authors report that one patient (1/30, 3%) "was withdrawn from therapy because of drug-seeking behavior …. "[212] This patient "complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day … and sought to obtain oral narcotics from other health care providers," although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.[213] The authors conclude "In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low," but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronics, Inc., the makers of the intrathecal pump.[214]

C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this

[210] *Id.* at p. 2484.
[211] Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. 1999;44(2), at p. 289.
[212] *Id.* at p. 292.
[213] *Id.* at pp. 295-296.
[214] *Id.* at p. 299.

case, they followed patients for 5 years.[215] The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,[216] and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude "There was no occurrence of opioid dependence, either physical or psychological…."[217]

D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.[218] The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.[219] The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.[220] Despite the absence of any method for detecting or measuring addiction risk, the authors concluded, "No instances of drug addiction or abuse were recorded."[221]

E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report "drug abuse/dependence" in less than 1% of their sample, but qualify this by saying, "none was considered definitely related to the treatment."[222] Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric disorders were excluded, no screening or detection instruments for opioid misuse or addiction were

[215] Hassenbusch, S, Stanton-Hicks, M, Covington, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. Journal of Pain and Symptom Management. 1995:10:527-543, at p. 529.
[216] *Id.* at p. 528.
[217] *Id.* at p. 536.
[218] McIlwain H, Ahdieh H. Safety , Tolerability , and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. Am J Ther. 2005;112:106-112, p. 106.
[219] *Id.* at p. 111.
[220] *Id.* at p. 108.
[221] *Id.* at p 109.
[222] Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. 2001;2(4):197-204. doi:10.1054/jpai.2001.25352, at p. 197.

described.[223] The authors report three cases of "drug abuse (2 moderate and 1 severe)"; two cases of "moderate physical drug dependence (as opposed to abuse)"; and "no reports of addiction."[224] Yet how these concepts were defined and the cases detected are not clarified. The study was supported by a grant from Janssen.[225] Despite these serious flaws, the authors concluded, "There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence that these fears are unfounded."[226] This conclusion does not follow from the evidence.

F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10 months between 1996-2002.[227] The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of Dellemijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.[228] A complete description of exclusion criteria was not provided; the authors stated only, "Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen."[229] No information is provided as to what constituted "contraindications to opioids;" and the exclusion for "opioids use outside the designated treatment regimen" inherently eliminates the population with the most obvious defining characteristic of addiction. The authors state, "Following discontinuation from the study, no patient complained of withdrawal symptoms or was

[223] *Id.* at p. 198.
[224] *Id.* at pp. 201-202.
[225] *Id.* at p. 197.
[226] *Id.* at p. 203.
[227] Mystakidou, Kyriaki, Parpa, Efi, Tsilika, Eleni, Mavromati A, Smyrniotis V, Georgaki, Stavroula, Vlahos L. Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain*. 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.
[228] *Id.* at p. 305.
[229] *Id.* at p. 299

found to display dependency"[230]; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.

G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (Oxycontin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy. The authors reported "6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse."[231] This appears to be the basis for the "3%" figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, "Patients with self-reported past or present substance or alcohol abuse" were excluded, as were patients with a "documented allergy to oxycodone or other opioids."[232] Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.[233]

H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.[234] Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were

[230] *Id.* at pp. 300-301.
[231] Portenoy, *et al.*, "Long Term Use," fn. 204, above, at p. 296.
[232] *Id.* at p. 288.
[233] *Id.* at p. 287.
[234] Zenz, Michael; Strumpf, Michael; Tryba M. Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. 1992:69-77, at p. 70.

discontinued for "lack of compliance;" and 8 died during the study period).[235] Zenz reported, "There were no cases of respiratory distress or addiction to opioids."[236] As in the studies described above, Zenz had no protocol to look for or record addiction or abuse. No details were provided as to the type of "noncompliance" that caused 10 patients to be discontinued, but "noncompliance" in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.

I. In summary, the seven studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy and from lack of any method to detect addiction or abuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.

j. Opioid manufacturers conveyed the misleading message that as long as doctors were prescribing opioids to patients in pain, the prescription pad conferred protection against patients becoming addicted. The false claim of low rates of addiction with prescription opioids when prescribed for pain had a significant impact on the increased likelihood that physicians would prescribe. Defendants successfully encouraged doctors into believing the risks of addiction were low, which directly contributed to increased prescribing, by promoting poor quality evidence highlighting low addiction rates among pain patients. Contrary to what Defendants claimed, opioid painkillers are as addictive as heroin purchased on a street corner, even when being prescribed by a doctor for a legitimate pain condition, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.

i. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled "Addiction Rare in Patients Treated with Narcotics," reported only four cases of addiction among 11,882 patients treated with opioids.[237] This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent.

[235] *Id.* at p. 73.
[236] *Id.* at p. 69.
[237] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

ii. Nonetheless, it was widely cited by doctors and medical organizations and frequently quoted by the pharmaceutical industry in its advertisements for opioids in the treatment of chronic pain, as proving that "less-than-1%" of patients receiving opioids for pain becomes addicted.

iii. Defendants' promotional messages continued to cite their "less-than-1%" claim, or that addiction with chronic opioid therapy was "rare," despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)

iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, "According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, i.e., addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients".[238] The same article also stated, "It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other 'addiction' studies described earlier, as they are both within the prevalence percentages derived from these studies".[239] However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain's 2008 analysis.

v. Also, Fishbain's 2008 review[240] included data from a 1992 study by Bouckoms, *et al.* , which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for "narcotics addiction".[241] Bouckoms also stated: "The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively".[242] Notably, the 0.03% figure in Bouckoms' text is based on the Porter and Jick 1980 Letter[243]—the only one of the 5

[238] Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.
[239] *Id.* at p. 81.
[240] Fishbain, *et al.*, "What Percentage," fn. 177, above.
[241] Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry. 1992. doi:10.3109/10401239209149570, at p. 185.
[242] *Id.* at p. 188.
[243] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

references that was *not* based on a population of patients treated with opioids for chronic pain.

vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their marketing and promotional statements beginning in the 1990s cited the inapt Porter and Jick study[244] of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the claim of "less than one percent" prevalence of addiction. I am not aware of any Defendants having issued a marketing or promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.[245] Nor am I aware of any such statements by Defendants that cited the range of "prevalence from 3.2% to a high of 16% for the possibility of addiction" reported by Fishbain in 1992.[246]

vii. Later publications also reported addiction rates that did not appear in the promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles[247] data synthesis: Manchikanti (2003),[248] Cowan (2003),[249] Adams (2006),[250] Fleming (2007),[251] Banta-Greene (2009),[252] Schneider (2009),[253] Edlund (2007),[254] Hojsted (2010),[255] Jamison (2010),[256]

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[244] *Id.*
[245] Bouckoms, *et al.*, "Chronic Nonmalignant," fn. 241, above, at p. 188.
[246] Fishbain, *et al.*, "Drug Abuse," fn 238, above, at p. 80.
[247] Vowles, *et al.*, "Rates of Opioid Misuse," fn. 153, above.
[248] Manchikanti et.al Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. J Ky Med Assoc 2003;101:511–17, at p. 511.
[249] Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med. 2003;4(4):340-351, at p. 340.
[250] Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. J Pain Symptom Manage. 2006;31(5):465-476, at p. 465.
[251] Fleming, *et al.*, "Substance Use Disorders," fn. 151, above, at p. 573.
[252] Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend*. 2009;104(1-2):34-42, at p. 37.
[253] Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag*. 2010;6(6):385-395, at p. 390.
[254] Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med*. 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.
[255] Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain*. 2010;14(10):1014-1020, at p. 1014.
[256] Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain*. 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

Passik (2011),[257] and Meltzer (2012),[258] which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively.

viii. With one exception, all of these studies showed addiction prevalence multiple times higher than the "less than one percent" figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.

ix. The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%,[259] which is consistent with the other data synthesized by Vowles. Because this distinction is important and not obvious, I provide the additional details below.

A. First, the data used in the Edlund 2007 study came from a nationally representative community sample, Healthcare for Communities (HCC). The sample consisted of 9,279 people who were interviewed to investigate self-reported opioid misuse and "problem" opioid misuse among users and non-users of prescribed opioids, as well as use/ "problem use" of other substances (illicit drugs other than opioids, alcohol). "Opioid misuse" was defined to mean either without a doctor's prescription, or in a larger amount or for a longer time than prescribed. "Problem opioid use" added criteria of tolerance and/or psychological or emotional problems due to drug use to the general "misuse" definition.[260]

B. This Edlund study did not provide any data on "addiction." Nevertheless, the Vowles data synthesis included a value of 0.7% for "addiction."[261] However, the Edlund definition of "problem opioid use" is consistent with Vowles' definition of "addiction" to mean a "[p]attern of continued use with experience of, or demonstrated potential for, harm, (e.g.,

[257] Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage*. 2011;41(1):116-125, at p. 116.
[258] Meltzer, E, Rybin, D, *et al.* Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. Pain Med. 2012 November; 13(11): 1436-1443, at 1437.
[259] Edlund, *et al.*, "Do Users Have Higher Rates," fn 254, above, at p. 651.
[260] *Id.* at pp. 649-650.
[261] Vowles, *et al.*, "Rates of Opioid Misuse," fn. 153, above, at p. 572, Table 2.

impaired control over drug use, compulsive use, continued use despite harm, and craving)."[262]

C. Further, the reference to "0.7%" in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in "*the total HCC sample*," (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, "Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, P<0.001."; emphasis added).[263]

D. In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund's "problem opioid misuse" as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.

E. Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been "7.3%, 17 out of 282" prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.

F. Finally, Edlund acknowledged, "Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates."[264] Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

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[262] *Id.* at p. 570.
[263] Edlund, *et al.*, "Do Users Have Higher Rates," fn. 254, at p. 651.
[264] *Id.* at p. 654.

x. Purdue's Power Point presentation dated September 12, 2014, is addressed to a potential business opportunity involving "Project Tango." The document identifies Tango as the "global leader in the pharmaceutical treatment of addiction," and further states, "Addiction treatment is a good fit and natural next step for Purdue," because "Pain treatment and addiction are naturally linked."[265] I agree that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was "less than 1%," or "rare," or "uncommon," and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy.

6. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between suicide and opioids. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

a. Through drug reps, key opinion leaders, and CME content, manufacturers of opioids conveyed the misleading message that there is no ceiling dose for opioids. In an article by Portenoy's 1986 co-author Foley and others they wrote "We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect."[266] This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED). To put that in perspective, the average heroin addicted individual consumes 100 morphine milligram equivalents daily. Meanwhile, there is no evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.[267]

b. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: "Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients

[265] PPLPC016000255303, produced natively at *14 and *8.
[266] Foley KM, Fins JJ, Inturrisi CE. A true believer's flawed analysis. *Arch Intern Med*. 2011. doi:10.1001/archinternmed.2011.166, at p. 867.
[267] Edlund, *et al.*, "Role of Opioid Prescription," fn. 25, above, at p. 557.

receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. … Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients."[268]

c. Dunn also noted that their study "provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses."[269] The study also provided important data on the relationship between fatal and non-fatal overdoses, in particular, that "[m]ore than 7 nonfatal overdoses events occurred for each fatal overdose" in the study cohort.[270]… "The inclusion of nonfatal overdoses improves understanding of the problem, because most previous work has examined only fatal overdoses. The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious."[271] These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017 would translate to over 100,000 nonfatal overdoses. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

d. A study by Bohnert *et al.* found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MEDs. Compared to the Reference dose of 1 to < 20 MED, the adjusted hazard ratio for 20 to < 50 MED was 1.88; for 50 to < 100 MED, the hazard ratio was 4.63; and at > 100 MED, the hazard ratio was 7.18; all three results were statistically significant. A similar pattern held for each of three diagnostic groups (substance use disorders, chronic pain, and cancer): "The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR =

[268] Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med*. 2010;152(2):85-92, at p. 85.
[269] *Id.* at p. 90.
[270] *Id.* at p. 89.
[271] *Id.* at p. 91.

6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%)."[109272] Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

e. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.[273]

f. The risk of addiction, like the risk of overdose and mortality, also increases in a dose-dependent manner. As previously stated, "Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially."[274] For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[275]

g. The link between suicide and opioids is undeniable and complex. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that "A reduction in the quantity of prescribed opioids may function as a 'means restriction' by reducing patients' access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients' access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity.

[272] Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 1315; Olsen, *et al.*, Pain relief that matters, fn 107, above.
[273] Gomes *et.al,* "Opioid Dose," fn. 124, above, at p. 686.
[274] Edlund, *et.al.* "Role of Opioid Prescription," fn. 25, above, at p. 561.
[275] *Id.* at pp. 559-560.

However, whether tapering changes the risk of either suicide or overdose is unknown."[276]

h. Opioids are associated with more adverse medical outcomes and increased mortality than non-opioid analgesics (NSAIDS),[277] contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDS) for pain are comparable.[278]

7. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as "breakthrough pain." There is no such thing as "pseudoaddiction," and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

a. Tolerance is the need for more and more of the drug to get the same effect. As the dose is increased to overcome tolerance to the pain relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with the drugs, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.[279] Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose.

b. Based on a single case report of a patient who engaged in drug-seeking behavior,[280] doctors were encouraged to conceptualize the patient's addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox, who went on to work at Purdue. The

[276] Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76

[277] Solomon DH, Rassen J a, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

[278] Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, nonopioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

[279] Lembke, *et al.*, "Weighing the Risks," fn. 3, above, at p. 987; Chou, *et al.*, "Effectiveness and Risks," fn. 60, above, at p. ES-25.

[280] Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989;36(3):363-366. http://www.ncbi.nlm.nih.gov/pubmed/2710565.

following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."[379]

Dated: March 25, 2019

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[379] Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.